Depression Leading to Suicide As An Adverse Effect of Metoclopramide

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Abstract

Metoclopramide (Reglan, Baxter Healthcare, Deerfield, Illinois) is a substituted benzamide derivative with therapeutic utility as a stimulant of upper gastrointestinal motility. Metoclopramide is prescribed widely for diabetic gastric stasis and nausea. Although many of metoclopramide's adverse effects are appreciated by both prescribing physicians and patients, depression can occur, sometimes with devastating results. We describe a case of suicide which was causally related to metoclopramide.

REPORT OF A CASE

The patient was a 70 year old Caucasian man who took metoclopramide for the nine months prior to his death from suicide. He had a two year history of documented sliding hiatal hernia with moderate gastroesophageal reflux; an upper GI study showed transient hold up of the barium pill at the level of a hiatal hernia. Medical history included hypertension, hyperlipidemia, bronchiectasis, chronic dysphagia, GERD, hiatal hernia, sick sinus syndrome/atrial fibrillation, and benign prostate hypertrophy. Thyroid panel was normal. The patient's father committed suicide when the patient was 4 years old, and there is little information about this, although the patient's widow thought that there were severe financial pressures involved. The patient did not smoke or use alcohol.

Metoclopramide was prescribed for difficulty swallowing food. Concurrent medications at that point were Zocor, Prenivil, and Protonix. The patient first complained to friends of depression on the third month of treatment with metoclopramide. At the sixth month of metoclopramide treatment, an antidepressant (Zoloft) was prescribed. There was no improvement in his depression. Following the use of Zoloft, three other antidepressant drugs (Prozac, Effexor and Celexa) were tried, also without improvement in his depression. The patient's depression became severe, he lacked motivation to do any physical activity, was increasingly tired, did not desire to interact with others, and slept excessively. According to his wife, the patient had been energetic and optimistic for the 47 years of their marriage prior to the start of metoclopramide. The patient's treating physician stated that his differential diagnoses included Parkinson's vs. Parkinson's with atypical depression pattern vs. early dementia. Thyroid levels were normal. The patient did not exhibit symptoms of akathesia, agitation or flat affect. No cognitive deficits were measured or noted.

Upon referral to a neurologist, it was determined that these symptoms were most likely secondary to metoclopramide use, that the patient was significantly depressed and needed psychiatric follow-up. No mention was given of the danger of suicide or need for protection. A few days later, the patient committed suicide by gunshot to the chest.

METHODS

The basis of this case report was a thorough review of the medical records, an interview with the patient's spouse, and a search of the current medical literature using Medline.

RESULTS

Using universally accepted algorithms for the determination of causal relatedness between medication and adverse effects, [1] metoclopramide was determined to be causally related to this suicide. The key bases for this association were:

1. Temporality: Lack of pre-metoclopramide depression or suicidal thoughts,
2. Temporality: Depression and suicide occurred after the start of metoclopramide,
3. Known adverse effect: depression (prescribing info), suicide ideation (peer-reviewed medical

literature),

4. Biological Plausibility: Metoclopramide has centrally nervous system actions, and is an antagonist of dopamine,

5. Biological Coherence: Does not conflict with what is known,

6. The absence of an alternative explanation.

DISCUSSION

The wide variety of both desired and adverse effects from metoclopramide stem from its ability to act both centrally (nausea) and peripherally (gastric motility), as an antagonist of dopamine, and sensitize gastric smooth muscle to the effects of acetylcholine stimulation. The CNS side effect profile of metoclopramide is broad, and includes drowsiness, extrapyramidal syndrome (dystonias, akathesia), depression, dizziness and insomnia. [2,3,4]

Metoclopramide is similar to two other benzamides - sulpiride and amisulpiride, which are antipsychotics available in England. In fact, metoclopramide itself has clinical antipsychotic efficacy. [5] Antipsychotic treatment has been identified as one of the factors responsible for the increased rate of suicide in schizophrenics, [6] so it follows that any drug with antipsychotic efficacy, and which can cause akathesia (such as metoclopramide) may cause an increased risk of suicide. The current prescribing information for metoclopramide includes a WARNING which states, “Mental depression has occurred in patients with and without prior history of depression. Symptoms have ranged from mild to severe and have included suicidal ideation and suicide. Metoclopramide should be given to patients with a prior history of depression only if the expected benefits outweigh the potential risks.” [2]

Clinicians have reported that akathesia can exacerbate psychopathology. [7] It is recognized that akathesia can be linked to both suicide and violence. [8, 9] A link between akathesia and violence, including homicide, following antipsychotic use has also previously been reported. [10,11,12]

Weddington and Banner identified a patient who developed an organic affective syndrome after administration of metoclopramide. [13] The syndrome was characterized by dysphoria, akathesia, depressed mood with suicidal ideation, insomnia, racing thoughts and labile affect. The symptoms increased within 30 minutes of each dose, and upon discontinuation of metoclopramide, the symptoms gradually resolved (challenge – dechallenge response). Although there have been perhaps eight case reports in the medical literature of depression thought to be causally related to metoclopramide use, to my knowledge this is the first published case of completed suicide caused by metoclopramide.

The DSM-IV defines a Substance-Induced Mood Disorder (SIMD) as

1. having evidence from the history, physical examination or laboratory findings of symptoms developing during, or within a month of substance (in this case, metoclopramide) intoxication or withdrawal, or the medication use is etiologically related,

2. does not occur exclusively during the course of a delirium,

3. the symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning,

4. with Depressive Features: if the predominant mood is depressed. Manic mixed features can also occur.8

Clearly, from this definition, the patient reported here had experienced a SIMD from metoclopramide toxicity. The patient did not experience a beneficial antidepressive response after treatments with three different antidepressants of the selective serotonin reuptake inhibitor (SSRI) class. This is not completely surprising, in that clinical experience and a number of recent articles point to a disappointing overall beneficial clinical response rate to SSRIs, only slightly greater (57.5%) than for placebo.[14] Increasing the dosage of SSRIs as a means to increase the clinical response often only leads to an increase in adverse effects, and (frequent) switching between SSRIs can lead to its own group of problems (discontinuation syndrome, toxicity).

Fisher and David reported that metoclopramide can interact with SSRI drugs to cause a Serotonin Syndrome.[15] This syndrome results from excessive stimulation of central and peripheral serotonergic receptors, and is characterized by changes in mental status, and motor and autonomic function. SSRI drugs are commonly used antidepressants, which have also been associated with agitation, aggression, and suicide. [2]

The two patients reported by Fisher and David were stable on SSRIs before the addition of metoclopramide, [15] whereas in the case reported here, SSRIs were given after depression had arisen from use of metoclopramide. There is no indication that the subject of the current report had developed a Serotonin Syndrome.

SSRI medication has clearly been linked with suicidal ideation and suicide.[16, 17]

During the first month of therapy, SSRI antidepressants in patients 66 years of age and older were associated with a nearly fivefold higher risk of completed suicide than other antidepressants. [18]It is possible in this reported case that the addition of SSRI medications may actually have exacerbated the metoclopramide-induced depression and precipitated the suicide. This is why prescribing physicians must be aware of the adverse effect potentials for all medications prescribed for patients, including drug-drug interactions; and must adequately warn their patients and patient families to anticipate problems and what actions to take. In this reported case, depression was caused by metoclopramide, and the appropriate treatment would have been discontinuation of metoclopramide, not the addition of a medication known to increase the risk of suicide. SSRIs do not have proven clinical efficacy, nor an indication to treat medication (for example, metoclopramide)-induced depression. In fact, there is preliminary imaging data which would suggest that medication-induced depression activates different regions of the brain than that of endogenous MDD (DH Marks et al, 2007 Submitted).

It is imperative that prescribing physicians remain informed and aware of as wide a pattern, as possible, of potential serious and severe adverse effects of the medications they prescribe. Warnings to patients and their families that new or worsening symptoms can represent adverse effects of prescribed medications, rather than a progression of the underlying disease state, can be life-saving.

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